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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Skyclarys (Omaveloxolone)
Treatment of Friedreich's ataxia
EU/3/18/2037

Sponsor: Reata Ireland Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Omaveloxolone
Other name(s)	Skyclarys, Omaveloxolone
International Non-Proprietary Name	Omaveloxolone
Tradename	Skyclarys
Orphan condition	Treatment of Friedreich's ataxia
Sponsor's details:	Reata Ireland Limited Block A George's Quay Plaza George's Quay Dublin 2 D02 E440 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Dr Stefan Blesse
COMP opinion	24 May 2018
EC decision	27 June 2018
EC registration number	EU/3/18/2037
Post-designation procedural history	
Transfer of sponsorship	Transfer from Dr Stefan Blesse to Granzer Regulatory Consulting & Services – EC decision of 07 November 2019 Transfer from Granzer Regulatory Consulting & Services to Reata Ireland Limited – EC decision of 02 August 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Thalia Marie Estrup Blicher/Tomas Radimersky
Applicant	Reata Ireland Limited
Application submission	28 November 2022
Procedure start	28 December 2022
Procedure number	EMA/H/C/006084/0000
Invented name	Skyclarys
Proposed therapeutic indication	Invented name is indicated for the treatment of Friedrich's ataxia Further information on Skyclarys can be found in the European public assessment report (EPAR) on the Agency's website: http://www.ema.europa.eu/en/medicines/human/EPAR/Skyclarys
CHMP opinion	14 December 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Gloria Maria Palomo Carrasco / Elisabeth Penninga
Sponsor's report submission	23 October 2023
COMP discussion	05-07 December 2023

COMP opinion (adoption via written procedure)	15 December 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- The intention to treat the condition with the medicinal product containing omaveloxolone was considered justified based on clinical data demonstrating delayed deterioration of neurological function;
- the condition is chronically debilitating and life-threatening due to ataxia, progressive disability that requires the use of wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy;
- the condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.
- The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Friedreich's ataxia (FA) is a progressive degenerative disorder affecting multiple organs and is caused by systemic insufficiency of the mitochondrial protein frataxin.

The clinical phenotype of FA represents a multisystem disease encompassing not only characteristic neurological features such as ataxia, dysarthria, areflexia, and sensory loss, but also diverse non-neurological features such as hypertrophic cardiomyopathy, kyphoscoliosis, foot deformities (pes cavus) and diabetes mellitus.

FA is mainly characterised by spinocerebellar degeneration and peripheral sensory neuropathy. The dorsal root ganglia (DRG) are particularly affected in FA with atrophy of the large-myelinated fibres. It is still unclear whether the peripheral neuropathy is a primary effect of the disease or the result of the DRG lesions.

Age and GAA1 repeat length are known as prognostic factors. One fifth of patients are younger than 5 years at onset. Disease onset before the age of 20 and cardiac involvement are associated with faster progression of neurological symptoms. Cardiac dysfunction as a consequence of dilated cardiomyopathy and arrhythmias is widely accepted as the most common cause of mortality in patients with FA. Severe pes cavus is present in up to 25% of the typical onset FA population (Reetz, 2018).

Frataxin mRNA is mainly expressed in tissues with high metabolic rate such as liver, kidney, neurons and heart. Most of the cases (96%) of FA are associated with homozygous GAA repeats within intron 1

of the frataxin (*FXN*) gene. Reduced levels of FXN lead to impaired iron-sulfur cluster biogenesis, lower mitochondrial respiration, impaired mitochondrial adenosine triphosphate (ATP) production, mitochondrial iron overload and the production of reactive oxygen species (ROS). This in turn is likely to cause lipid peroxidation and cell death. The levels and activity of Nrf2, a key player for antioxidant gene expression upon translocation to the nucleus, are suppressed in response to insufficient FXN levels, as it has been seen in cells from patients with FA and several non-clinical models, leading to impaired Nrf2 signalling. This not only impairs antioxidant response, but also contributes to the ROS production. Increased oxidative stress markers are one of the most studied hallmarks of the disease.

The approved therapeutic indication *"Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older"* falls within the scope of the designated orphan condition "Treatment of Friedreich's ataxia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Clinical symptoms of FA are characterised by progressive spinocerebellar ataxia with the first symptoms including dysarthria and gait instability with imbalance and thereby a risk of falls, followed by loss of fine motor skills, dysmetria, intention tremor, and dysphagia.

The onset of clinical symptoms of FA is before the age of 25 years in most cases, with an average age of around 10–15 years, but age of onset may be as low as 2 years. Typically, within 10 to 15 years, FA patients cannot walk, sit, or stand without support (Pandolfo, 2008) and become wheelchair bound (Delatycki and Corben, 2012). Cardiomyopathy is seen on echocardiography in approximately 65% of patients in cross-sectional studies.

Life-expectancy in FA patients with cardiomyopathy is significantly reduced to around 30–40 years. Definite or probable cardiac dysfunction is the most common cause of death seen in around 60% of all FA patients.

FA is therefore considered both chronically debilitating and life threatening.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 0.5 per 10,000 persons for the condition Friedreich's ataxia.

This estimate is the same as the one accepted by the COMP during the initial orphan designation in February 2018. The sponsor has conducted a comprehensive literature search for any updates on the prevalence of FA in the EU/EEA, considering publications from 2018 onward.

A recent systematic literature review was identified summarising the available prevalence data worldwide (Buesch, 2022). According to the authors, the current study is the first to consider the method of diagnosis, i.e., clinical versus molecular, when reviewing estimates published within the literature. Of the 22 studies included in this systematic review, 17 studies related to the European Economic Area (EEA), covering the period 1910-2014. These studies are presented in Table 1.

Table 1. Prevalence Studies from EEA Countries Included in the Systematic Review by Buesch, 2022

Country, (period)	Region	Study setting	Diagnostic method	Calculated prevalence per 100,000	Reference
Finland (1997–2001)	Nationwide	Multiple search strategies	Clinical and molecular	0.10	Juvonen, 2002
Italy (NR)	Padua	Multiple search strategies	Clinical and molecular	0.59	Zortea, 2004
Norway (2002–2008)	Southeast	Multiple search strategies	Clinical and genetic	0.15	Erichsen, 2009
Portugal (1994–2004)	Nationwide	Multiple search strategies	Clinical and/or molecular	1.00	Coutinho, 2013
Greece (1995–2012)	-	National reference / referral centers, diagnostic center	Clinical and/or molecular	0.87	Koutsis, 2014
Norway (2011–2014)	Nationwide	Multiple search strategies	Clinical and molecular/ genetic	0.52[a]; 0.57[b]	Wedding, 2015
Iceland (1954–1963)	-	NR	NR	1.07	Gudmundsson, 1969
Norway (1952–1967)	Sogn-og-Fjordane, Hordaland, and Rogaland; Western Norway	One regional center	Clinical	0.97	Skre, 1975
Italy (1910–1964)	-	Multiple centers	Clinical	N/A	Romeo, 1983*
Italy (1970–1980)	Cuneo (in Piedmont), North Italy	Multiple search strategies	NR	1.27	Pinessi, 1984
Italy (NR)	Reggio Emilia	NR	Clinical	1.42	Lucci, 1984
Italy (NR)	South	NR	NR**	1.10	Romeo, 1984
Italy (1945–1982)	Torino	Multiple search strategies	Clinical	0.99	Brignolio, 1986
Italy (1945–1984)	Torino, Cuneo, Vercelli, Asti of the Piedmont region, and Aosta in the Valle d'Aosta region; northwest Italy	Multiple search strategies	Clinical	1.22	Leone, 1990
Spain (1974–1986)	Cantabria, North Spain	One center/hospital	Clinical	4.71	Polo, 1991
Italy (1979–1989)	Molise	Multiple search strategies	Clinical	2.1	Filla, 1992
Spain (NR)	Valencia (incl Valencia, Ali cante and Castellón)	Regional reference center	Clinical	3.83	López-Arlandis, 1995***

Abbreviations: EEA=European Economic Area; NR=not reported; N/A=not applicable

* Based on consanguinity analysis

** Study time period precedes the availability of molecular diagnostics.

*** Children only

a - Prevalence among ethnic Norwegians b - Prevalence among all Norwegians.

Source: Adapted from Buesch, 2022

The prevalence estimates for the EEA studies included in this systematic review range from 0.01/10,000 in a nationwide study from Finland between 1997 and 2001 (Juvonen, 2002) and 0.47/10,000 in a single-centre study from Spain between 1974 and 1986 (Polo, 1991). The results of the current systematic review by Buesch, 2022 are consistent with the earlier systematic review by Ruano, 2014. Furthermore, the highest prevalence estimates included in the systematic review by Buesch, 2022, 3.83 and 4.7 per 100,000, originate from two single-site studies in Spain that were published in the 1990's (López-Arlandis, 1995; Polo, 1991), while the three most recent European studies, conducted in Portugal, Greece and Norway, report prevalence that is not higher than 1.0 per 100,000 (Coutinho, 2013; Koutsis, 2014; Wedding, 2015). In conclusion, review of updated literature does show a varying prevalence; however,

a conservative estimate is reflected by the 2 publications reflecting Spain (Polo, 1991; López-Arlandis, 1995) and are consistent with the original basis of the prevalence calculation in FA, estimating 0.5 in 10,000 persons.

The COMP agreed with the sponsors prevalence calculation and final estimate of 0.5 per 10,000 persons.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no authorised pharmacological treatment options specifically indicated for the treatment of FA in Europe.

In the US, omaveloxolone (SKYCLARYS) received Food and Drug Administration (FDA) approval on 28 February 2023 for the treatment of FA in adults and adolescents aged 16 years and older.

The most recent consensus clinical management guidelines consider that FA remains a non-treatable ataxia and are only able to provide recommendations for the use of non-FA specific interventions in the management of the symptoms of FA including palliative treatment (Corben, 2022; de Silva, 2019). Symptoms in patients with FA are managed by multidisciplinary teams, including neurologists, cardiologists, physical therapists, and others, each of whom may use both non-pharmacological and pharmacological interventions. There is a spectrum of non-FA specific interventions referenced in current guidelines (Corben, 2022; de Silva, 2019).

Significant benefit

Not applicable.

4. COMP position adopted on 15 December 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of Friedreich's ataxia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to ataxia, progressive disability requiring use of wheelchair, and life-threatening due to hypertrophic cardiomyopathy leading to cardiac failure;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;

- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Skyclarys, omaveloxolone for treatment of Friedreich's ataxia (EU/3/18/2037) is not removed from the Community Register of Orphan Medicinal Products.